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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,542	11/30/2001	John D. McNeish	PC10897ADAM	1000

7590 12/24/2003

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,542	MCNEISH ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6 and 7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment filed on 09/23/2003 has been entered. Claims 2,4,5 and 8-14 have been canceled. Claims 1,3,6 and 7 have been amended, are pending and are under consideration in the instant action.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1,3,6 and 7 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant's arguments with respect to the rejection based on the lack of description of transgenic knockout mice produced through gene-targeting in somatic cells followed by nuclear transfer (see paragraph bridging pages 25-26 of the specification) are not considered persuasive and this aspect of the rejection is maintained for the reasons of record set forth in the previous office action mailed 06/08/2003 (see pages 2-4) and reiterated below.

The claims, as written, encompass genetically modified mice generated through somatic cell nuclear transfer. As stated in the previous office action, the phenotype of animals generated by nuclear transfer is highly unpredictable because they are often abnormal with no consistent pattern of abnormality to indicate the cause of the defects (Dinnyes, 2002, Cloning and Stem

Cells, Vol. 4, page 87, col. 1, 3rd para; McGreath, 2000, Nature, Vol. 405, para. Bridging pp. 1067-1068). Thus, if one skilled in the art were to generate the claimed mouse using somatic cell nuclear transfer, it is likely that the mouse obtained will exhibit phenotypes unrelated to the RAMP1 gene disruption.

Applicants argue that the addition of the phenotypic limitation of "nondetectable RAMP1 polypeptide activity" overcomes this rejection. This phenotype does not fulfill the requirement that the claimed invention be described in the specification in such a way as to reasonably convey that the inventors had possession of the claimed invention. Functional disruption of a gene, by definition, results in nondetectable activity of the disrupted gene. The added claim limitation does not overcome the failure of the specification to describe the phenotype of the mouse derived by somatic cell nuclear transfer as encompassed by the claims.

2) In light of Applicant's amendment to claims 6-8, the aspect of the rejection with respect to the failure of the specification to describe more than one RAMP1 gene is withdrawn.

Enablement

Claims 1 and 3 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants arguments have been fully considered and are partially persuasive as set forth below.

1) The aspect of this rejection based on the failure of the specification to enable using a genetically-modified mouse wherein said mouse comprises a disruption of the RAMP1 gene

wherein the mouse exhibits any phenotype is maintained for reasons of record set forth on pages 5-7 of the previous office action.

The amended claim 1 recites the limitation "wherein said mouse exhibits nondetectable RAMP1 polypeptide activity". The claims read on a mouse lacking RAMP1 activity wherein the mouse can exhibit any observable phenotype as a result a lack of RAMP1 function, including a wild-type phenotype and phenotypes other than the described altered aminotransferase, alanine aminotransferase, and creatine kinase activities (refer to specification page 32. The specification teaches a mouse generated by targeted gene disruption of the RAMP1 gene in ES cells wherein the mouse exhibits altered aminotransferase, alanine aminotransferase, and creatine kinase activities, which are associated with muscle and/or liver cell damage (page 32, lines 16-20).

Applicant argues that the amended claim 1 now includes a phenotypic limitation that the mice do not exhibit RAMP1 polypeptide activity and this limitation overcomes the enablement rejection. The asserted utility for the claimed mice is to screen for modulators of RAMP1 activity to identify potential drugs to treat cardiovascular or skeletal muscle myopathies (page 32, lines 27-30). The limitation of failing to exhibit RAMP1 polypeptide activity does not require that the mouse exhibit any attributes that would enable the skilled artisan to use said mouse. The evidence of record fails to correlate non-detectable levels of RAMP1 activity with a disease or disorder. One of skill in the art would not know what to assess in carrying out a screen for modulators of RAMP1 activity. For example, the art at the time of filing held that mice with elevated levels of creatine kinase displayed phenotypes associated with muscular dystrophy (Chapman, 1989, PNAS, Vol. 86, pages 1292-1296). The mice exhibiting muscular dystrophy phenotypes could be used to screen for mutations affecting muscular dystrophy because a

detectable and observable phenotype existed that one could use as a basis for screening. Claims 1 and 3, encompass mice exhibiting any observable phenotype, including wild-type that results from a lack of RAMP1 activity. The skilled artisan would not know how to use a mouse that merely lacks RAMP1 activity wherein the lack of RAMP1 activity results in any observable phenotype, including wild-type, to screen for drugs that treat the effects of loss of RAMP1 activity.

2) Amended claims 6 and 7 now encompass a genetically-modified totipotent, cultured murine ES cell. The term murine encompasses species other than mouse, including rat. The specification teaches a totipotent mouse ES cells (page 24, lines 22-32) and other species of ES cells that are pluripotent (page 23, line 33-page 24, line 7). The specification fails to teach making a totipotent murine ES cell other than mouse totipotent ES cells. The art at the time of filing held that totipotent ES cells that can contribute to the germ line and thus have to potential to form all cell types, have not been isolated for any species other than mouse (refer to Campbell and Wilmut, 1997, Theriogenology, vol. 47, pp, 63-72, specifically, page 65; Pera (2000, Journal of Cell Science, Vol. 113, pages 5-10, specifically page 6, column 2, last paragraph). Therefore, it would require undue experimentation for one of skill in the art at the time the invention was made to make the totipotent murine ES cells encompassed by the claims.

3) Claims 1 and 7 have been amended to limit the scope of the claims to the RAMP1 gene. Claims 2 and 8 have been cancelled. In light of applicant's amendments, the rejection of claims 1-3 and 6-8 as lacking enablement for claims encompassing any RAMP1 gene is withdrawn.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Applicant has cancelled claim 8 and amended claim 6 to include the term "cultured" which indicates the claimed cells are cells in vitro. In light of applicants' amendment, the rejection of claims 6-8 under 35 USC 112, 2nd paragraph has been withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 2 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (Scientific American, 1994, Vol. 270, pages 34-41) in view of Hussman (Mol. Cell. Endocrin., 2000, Vol. 162, pp 35-43) for the reasons of record set forth on pages 8-9 of the previous office action and reiterated below.

Capecchi taught a mouse whose genome comprised a disruption in the HoxA-3 gene by insertion of a selective marker gene into the HoxA-3 gene. Capecchi differs from the claimed invention in that the targeting construct does not disrupt the RAMP1 gene.

However, at the time the claimed invention was made, Hussman taught the nucleic acid sequence of the mouse RAMP1 gene and RAMP1 coding region (full text).

One of ordinary skill in the art would have been sufficiently motivated to replace the Hox3A gene with the RAMP1 gene, as it was an art recognized goal to determine the

physiological role of a gene of interest by the generation of a knockout mouse. One of ordinary skill in the art would have been sufficiently motivated to disrupt the RAMP1 gene as a means of determining whether it has a role in regulating receptor systems other than the calcitonin-like receptor.

Applicants argue that one of skill in the art would not be able to predict that the RAMP1 knockout mouse would be viable and thus it would not have been obvious to make the claimed mouse. Applicant cites Zambrowicz (Nature, 2003, Vol. 2, pages 38-51) as teaching that many genes, when mutated, lead to embryonic lethality. Applicant refers to the 7 embryonic lethal gene targets in Table 8, which lists approximately 32 targets for which knockout information is available, as support for the idea that a RAMP1 knockout mouse may have been predictably embryonic lethal. This argument is not persuasive. The 32 targets listed in Table 8 are the targets of the 100 best selling drugs of 2001 and are not representative of the vast number of knockout mice that have been generated. In fact, according to http://www.bioscience.org/knockout/knochome.htm (list compiled in 1998), of over 300 knockout mice randomly entered into the database, only 39 exhibit prenatal mortality. Based on the art of record and the known characteristics and activity of RAMP1, there is no evidence suggesting that mutation of RAMP1 would result in embryonic lethality. Therefore, it cannot be predicted prior to generating a RAMP1 knockout mouse that the mouse would suffer from embryonic lethality.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on Mon-Weds 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on Mon-Weds 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Note: After January 13, 2004, the Examiner may be reached at (571) 272-0725, and should the Examiner be unavailable, inquiries may be directed to Deborah Reynolds, SPE of Art Unit 1632 at (571) 272-0734.

Valarie Bertoglio
Examiner
Art Unit 1632

PETER PARAS
PATENT EXAMINER